

AMENDMENTS TO THE CLAIMS

- 1-5. (Canceled)
6. (Previously Presented) The recombinant inhibitor protein, or inhibiting fragment thereof, which inhibits a kallikrein, of claim 39, wherein the kallikrein is hK2 kallikrein.
- 7-16. (Canceled)
17. (Currently Amended) A pharmaceutical composition comprising the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 ~~or 40~~, and a pharmaceutically acceptable carrier.
- 18-27. (Canceled)
28. (Currently Amended) A method for producing the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39, comprising
- a) selecting a polynucleotide sequence encoding ~~[[a]] the~~ modified Reactive Serpin Loop (RSL) which inhibits ~~[[said]] the~~ Kallikrein by phage displayed library screening;
 - b) introducing ~~[[said]] the~~ polynucleotide sequence into a sequence encoding ~~[[a]] the~~ α -1 antichymotrypsin (ACT) serpin, so as to obtain ~~[[a]] the~~ recombinant inhibitor protein;
 - c) allowing expression of ~~[[said]] the~~ recombinant inhibitor protein in a cell expression system under suitable conditions; and
 - d) recovering ~~[[said]] the~~ recombinant inhibitor protein.
29. (Canceled)

30. **(Previously Presented)** The method of claim 28, wherein the suitable conditions comprise culturing the cell expression system at a temperature between 10-40°C during 10-30 hours.

31. **(Previously Presented)** The method of claim 30, wherein the suitable conditions comprise a temperature of 16°C during 16 hours.

32. **(Previously Presented)** The method of claim 28, wherein step d) is achieved by separation after extraction of the recombinant inhibitor protein, or inhibiting fragment thereof, from the cell expression system.

33. **(Previously Presented)** The method of claim 32, wherein the separation of the recombinant inhibitor protein, or inhibiting fragment thereof, is achieved by affinity chromatography.

34-35. **(Canceled)**

36. **(Previously Presented)** The method of claim 28, wherein the cell expression system is a bacterial cell.

37. **(Canceled)**

38. **(Previously Presented)** A diagnostic kit for the detection of a kallikrein in a specimen comprising the recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39.

39. **(Currently Amended)** A recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising [[a]] an α -1 antichymotrypsin (ACT) serpin sequence with a modified Reactive Serpin Loop (RSL) having an amino acid substitutions substituted sequence within the P6-P'6 interval, which result in

increased binding affinity for the kallikrein, wherein ~~at least one of~~ the amino acid substitutions ~~replaces at P1~~ ~~[[with]]~~ is an arginine (R) ~~or a lysine (K)~~ and creates a substituted P1-P'1 scissile bond wherein the recombinant inhibitor protein, or an inhibiting fragment thereof, comprises the amino acid substituted sequence within the P6-P'6 interval selected from the group consisting of
the P3-P'2 pentapeptide SSRTE (SEQ ID NO:23),
the P3-P'2 pentapeptide KTRSN (SEQ ID NO:24),
the P4-P'1 pentapeptide ISPRS (SEQ ID NO:25),
the P4-P'1 pentapeptide GVFRS (SEQ ID NO:26),
the P4-P'1 pentapeptide GTVRS (SEQ ID NO:27),
the P4-P'1 pentapeptide ETKRS (SEQ ID NO:28),
the P3-P'2 pentapeptide LGRSL (SEQ ID NO:29),
the P3-P'2 pentapeptide RGRSE (SEQ ID NO:30),
the P2-P'3 pentapeptide RRSID (SEQ ID NO:31),
the P3-P'2 pentapeptide VLRSP (SEQ ID NO:32),
the P3-P'2 pentapeptide PFRSS (SEQ ID NO:33),
the P1-P'4 pentapeptide RSGSV (SEQ ID NO:34),
the P4-P'1 pentapeptide ARARS (SEQ ID NO:35),
the P3-P'2 pentapeptide SDRTA (SEQ ID NO:36),
the P3-P'2 pentapeptide KLRTT (SEQ ID NO:37),
the P1-P'4 pentapeptide RAAMM (SEQ ID NO:38),
the P2-P'3 pentapeptide TRAPM (SEQ ID NO:39),
the P3-P'2 pentapeptide DVRAA (SEQ ID NO:40),
the P3-P'2 pentapeptide PGRAP (SEQ ID NO:41),
the P4-P'1 pentapeptide VESRA (SEQ ID NO:42),
the P2-P'3 pentapeptide ARASE (SEQ ID NO:43),
the P4-P'1 pentapeptide TLQRV (SEQ ID NO:44),
the P4-P'1 pentapeptide RLERV (SEQ ID NO:45),
the P2-P'3 pentapeptide ERVSP (SEQ ID NO:46),
the P4-P'1 pentapeptide SSPRV (SEQ ID NO:47),

the P1-P'4 pentapeptide RVGPY (SEQ ID NO:48),
the P4-P'1 pentapeptide PSARM (SEQ ID NO:49),
the P3-P'2 pentapeptide RGRMA (SEQ ID NO:50),
the P3-P'2 pentapeptide TVRMP (SEQ ID NO:51),
the P2-P'3 pentapeptide LRMPT (SEQ ID NO:52),
the P2-P'3 pentapeptide HRMSS (SEQ ID NO:53),
the P1-P'4 pentapeptide RPOEL (SEQ ID NO:54),
the P2-P'3 pentapeptide VRPLE (SEQ ID NO:55),
the P3-P'2 pentapeptide SGRLA (SEQ ID NO:56),
the P4-P'1 pentapeptide GTLRF (SEQ ID NO:57),
the P3-P'2 pentapeptide QWRNS (SEQ ID NO:58),
the P1-P'4 pentapeptide RNDKL (SEQ ID NO:59),
the P2-P'3 pentapeptide MRNRA (SEQ ID NO:60),
the P2-P'3 pentapeptide TRDSR (SEQ ID NO:61),
the P4-P'1 pentapeptide TGSRD (SEQ ID NO:62), and
the P4-P'1 pentapeptide IMSRQ (SEQ ID NO:63).

40. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[63]] 39, wherein the ~~kallikrein~~ is kallikrein hK2 modified RSL having amino acid substitutions is selected from the group consisting of amino acids 367 to 378 of SEQ ID NO:6 and SEQ ID NO:12.

41. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39, wherein the amino acid ~~substitutions are~~ substituted sequence within the P6-P'6 interval is selected from the group consisting of
the RSL of MD820 (SEQ ID NO: 16),
the RSL of ACT62 (SEQ ID NO:17),
the RSL of MD83 (SEQ ID NO:18),
the RSL of MD67 (SEQ ID NO:19),
the RSL of MD61 (SEQ ID NO:20),
the RSL of MD518 (SEQ ID NO:21), and

the RSL of MDCI (SEQ ID NO:22).

42. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[63]] 39, wherein the pentapeptide is a substrate peptide selected by said kallikrein using a phage-displayed random pentapeptide library.

43-50. **(Canceled)**

51. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P3-P'2 ~~comprises an~~ amino acid sequence selected from the group consisting of

SSRTE (SEQ ID NO:23),

KTRSN (SEQ ID NO:24),

LGRSL (SEQ ID NO:29),

RGRSE (SEQ ID NO:30),

VLRSP (SEQ ID NO:32),

PFRSS (SEQ ID NO:33),

SDRTA (SEQ ID NO:36),

KLRTT (SEQ ID NO:37),

DVRAA (SEQ ID NO:40),

PGRAP (SEQ ID NO:41),

RGRMA (SEQ ID NO:50),

TVRMP (SEQ ID NO:51),

SGRLA (SEQ ID NO:56), and

QWRNS (SEQ ID NO:58), and

SEQ ID NO:67.

52. **(Canceled)**

53. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P4-P'1 ~~comprises an amino acid~~ sequence selected from the group consisting of

ISPRS (SEQ ID NO:25),
GVFRS (SEQ ID NO:26),
GTVRS (SEQ ID NO:27),
ETKRS (SEQ ID NO:28),
ARARS (SEQ ID NO:35),
VESRA (SEQ ID NO:42),
TLQRV (SEQ ID NO:44),
RLERV (SEQ ID NO:45),
SSPRV (SEQ ID NO:47),
PSARM (SEQ ID NO:49),
GTLRF (SEQ ID NO:57),
TGSRD (SEQ ID NO:62),
IMSRQ (SEQ ID NO:63), and
PFRKI (SEQ ID NO: 66).

54. **(Canceled)**

55. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P2-P'3 ~~comprises an amino acid~~ sequence selected from the group consisting of

RRSID (SEQ ID NO:31),
ARASE (SEQ ID NO:43),
ERVSP (SEQ ID NO:46),
LRMPT (SEQ ID NO:52),
HRMSS (SEQ ID NO:53),

VRPLE (SEQ ID NO:55),
MRNRA (SEQ ID NO:60),
TRDSR (SEQ ID NO:61), and
LRSRA (SEQ ID NO: 68).

56. **(Canceled)**

57. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, wherein the amino acid substituted sequence within the P6-P'6 interval is a P1-P'4 ~~comprises an amino acid~~ sequence selected from the group consisting of

RSGSV (SEQ ID NO:34),
RAAMM (SEQ ID NO:38),
RVGPY (SEQ ID NO:48),
RPQEL (SEQ ID NO:54), and
RNDKL (SEQ ID NO: 59).

58-67. **(Canceled)**

68. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim 39 or 40, ~~wherein the amino acid substitutions are modified by further~~ comprising at least one additional substrate active site sequence modification.

69. **(Currently Amended)** The recombinant inhibitor protein, or inhibiting fragment thereof, of claim [[65]] 39, ~~wherein the substituted pentapeptide sequences are modified by further~~ comprising at least one additional substrate active site sequence modification.

70. **(New)** A method for identifying a recombinant inhibitor protein comprising a modified Reactive Serpin Loop, or inhibiting fragment thereof, which inhibits a Kallikrein, comprising

- a) selecting a polynucleotidic sequence encoding the modified Reactive Serpin Loop (RSL) which inhibits the Kallikrein by phage displayed library screening;
- b) introducing the polynucleotidic sequence into a sequence encoding the α -1 antichymotrypsin (ACT) serpin, so as to obtain the recombinant inhibitor protein;
- c) allowing expression of the recombinant inhibitor protein in a cell expression system under suitable conditions;
- d) recovering the recombinant inhibitor protein; and
- e) assaying the recombinant inhibitor protein for its ability to inhibit the activity of the kallikrein.

71. (New) The method of claim 70, wherein the suitable conditions comprise culturing the cell expression system at a temperature between 10-40°C during 10-30 hours.

72. (New) The method of claim 71, wherein the suitable conditions comprise a temperature of 16°C during 16 hours.

73. (New) The method of claim 70, wherein step d) is achieved by separation after extraction of the recombinant inhibitor protein, or inhibiting fragment thereof, from the cell expression system.

74. (New) The method of claim 32, wherein the separation of the recombinant inhibitor protein, or inhibiting fragment thereof, is achieved by affinity chromatography.

75. (New) The method of claim 28, wherein the cell expression system is a bacterial cell.

76. (New) The method of claim 28, wherein the fragment is at least 40% of the length of the native ACT amino acid sequence.

77. (New) The method of claim 28, wherein the fragment is at least 70% of the length of the native ACT amino acid sequence.

78. (New) The method of claim 28, wherein the fragment is at least 80% of the length of the native ACT amino acid sequence

79. (New) The method of claim 28, wherein the fragment is at least 90% of the length of the native ACT amino acid sequence.